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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/595,044	04/07/2006	Anne Angelillo-Scherrer	50304/009003	1775

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CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER	
DEBERRY, REGINA M	
ART UNIT	**PAPER NUMBER**
1647	

NOTIFICATION DATE	DELIVERY MODE
09/12/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/595,044	ANGELILLO-SCHERRER ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-30* is/are pending in the application.

4a) Of the above claim(s) *28 and 29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-27 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 January 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/13/06, 2/23/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Status of Application, Amendments and/or Claims

The amendment, filed 13 January 2006, has been entered in full.

Applicant's election without traverse of Group I (claims 21-27 and 30; drawn to a method of administering a Gas6 compound and erythropoietin) in the reply filed on 23 May 2008 is acknowledged.

Claims 28 and 29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Group, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 23 May 2008. Claims 21-27 and 30 are under examination.

Information Disclosure Statement

The information disclosure statement(s) (IDS) (filed 13 January 2006 and 23 February 2006) were received and comply with the provisions of 37 CFR §§1.97 and 1.98. They have been placed in the application file and the information referred to therein has been considered as to the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 26 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 26 recites the limitation "wherein said patient susceptible to the adverse side-effects of EPO". Claim 26 depends from claim 24. There is insufficient antecedent basis for this limitation in claim 26.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-27 and 30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification states that the present invention is based on a first observation that growth arrest-specific gene 6 (Gas6) expression is required for the development of sufficient erythroid reserves and to ensure an adequate hematopoietic response to an anemic challenge in human and/or mammals. The specification states that Gas6 is a new member of the vitamin K-dependent protein family (page 3). The specification states that it was found that treatment with a Gas6 compound can provide protection against anemia induced by hemolysis (page 5, lines 24-25). The specification states

that Gas6 was protective against anemia but did not result in the above-average hematocrit levels (page 6, lines 23-32). The specification states that Gas6 can be used for the treatment or prevention of anemia in patients for which treatment with erythropoietin (EPO) is contra-indicated (page 7, lines 1-10). Example 7 employs the use of mice; a wildtype and a Gas6-/- knockout mouse. The mice were treated with PHZ to induce anemia. The administration of recombinant EPO and Gas6 alone caused an increase in hematocrit in the both the wildtype mouse and Gas6 knockout mouse (Figure 4A and 4B). Figure 5 teaches the hematocrit levels in a mouse model for chronic anemia after administering recombinant EPO protein alone or recombinant EPO protein and recombinant Gas6 protein. Figure 5 shows increased hematocrit levels at day 4 after administering EPO and Gas6.

The instant claims, as recited, are not enabled because of the following reasons:

1. The specification is not enabling for the limitations “cure” or “prevent” (i.e. claim 21). To cure or prevent means to completely stop a condition from occurring. “Curing” and “preventing” are not relative terms, it is total. A very high degree of evidence is required, which is accepted in the art, that an absolute protection from the pathology exists over an extended period of time.

2. The specification fails to teach a synergistic rescue effect on erythropoiesis (i.e. claim 21). The Examiner understands synergy to be a state where the whole is greater than the sum of the parts. For example, Compound A causes a 10% increase in hair growth. Compound B causes a 15% increase in hair growth. When both compounds are combined together; a synergistic effect would be a hair growth

percentage that is significantly greater than the expected 25%. A synergistic effect of erythropoiesis was not seen.

A synergistic effect of increased hematocrit levels was seen, ***but*** **this effect was only seen when recombinant Gas6 protein and recombinant EPO protein were administered to Gas6-/- knockout mice treated with PHZ to induce anemia** (Figure 4B). The increased hematocrit synergistic effect **was not seen** in wildtype mice treated with PHZ to induce anemia or in any other anemic mouse model. The general patient populations would not have a knockout for the Gas6 gene, thus it is unclear how this effect would not be applicable to the claimed treatment.

3. The specification fails to demonstrate that anemia has been treated (i.e. claim 21). The instant examples measure hematocrit levels, but fail to examine reticulocyte hemoglobin content. The specification states that hematocrit levels can be used as a measure for the *condition* of red blood cells and the percentage of the volume of blood occupied by erythrocytes, but does not teach that hematocrit levels, ***alone***, can be used to discern *in vivo* erythropoiesis, which is the production of erythrocytes. For example, Ohls (Italian Journal of Pediatrics, Vol. 28, No. 5, pages 337-338; October 2002) teaches the use of reticulocyte hemoglobin content to discern how iron replacement affects erythropoiesis in pre-term infants. The instant specification has not established that hematocrit levels are tantamount to erythropoiesis levels.

4. The specification fails to teach a portion of an effective amount of EPO normally required to treat anemia, thereby ensuring a reduced risk of adverse side effects (i.e. claims 23-26). The specification states that target hematocrit levels are

usually around 41 to 51 % for healthy males and 35 to 45% for healthy females. However, the hematocrit levels rise well over 50% when EPO and Gas6 are administered to the mice. Furthermore, claim 25 is drawn to a method wherein said patient is susceptible to the side-effects of EPO and for which treatment with EPO is contra-indicted. Contra-indicate or contra-indication is defined as something (i.e. a condition or disease) that makes a particular treatment or procedure inadvisable. Indeed the specification teaches the term to mean that the adverse side effects of EPO would be more detrimental than for person for which treatment with EPO is not contra-indicted (page 16, lines 20-28). A high hematocrit would be an adverse side effect (Figures 4 and 5).

5. The specification fails to address the confusing fine line between demonstrating increased synergistic hematocrit levels (via administering Gas6 and EPO) to establish erythropoiesis, but not having increases in hematocrit levels, which would be detrimental.

6. Lastly, the specification is not enabled for analogues, mutants, variants or derivatives of Gas6 compounds, Gas6 protein or EPO protein. The specification states that the reference to Gas6, a mutant, variant or derivative thereof (generally referred to herein as Gas6 compounds) includes the Gas6 protein as encoded by the human Gas6 gene, any proteins having a modified amino acid sequence, whereby this modification does not detrimentally affect the activity of Gas6 described herein. The specification states that Gas6 includes species, specific homologs or orthlogs of Gas6 as well as truncations, deletions, point mutations, substitutions or other modifications made by

man (page 10). The disclosure fails to teach other species of Gas6. The disclosure provides no guidance as to which regions of the Gas6 protein would be tolerant of modification and which would not, and it provides no working example of any variant sequence which would be within the claims. It is in no way predictable that randomly selected mutations, deletions, etc. would afford a protein having activity comparable to the one disclosed. The specification states that maintenance of the activity of a Gas6 protein with a modified amino acid can be compared by determining the changes in hematocrit levels of such modified proteins, when compared to wildtype protein (page 10, lines 15-32). This is not found persuasive. It would require an indeterminate quantity of fundamentally unpredictable investigational experimentation of the skilled artisan to generate the infinite number of derivatives encompassed by Gas6 compounds, Gas6 protein analogue, mutant, variant or derivatives thereof and screen same for activity.

The specification states that EPO includes analogues, mutants, variants or derivatives thereof. While EPO is a well-characterized protein, the specification does not place any limit on the number of nucleotides substitutions, deletions, insertions and/or additions that may be made to EPO and still retain activity. For sequences having one or two substitutions, for example, the artisan would reasonably expect that many of the possible variants would retain functional properties comparable to those of the unmodified protein, and it would require only routine manipulations to make and test a reasonably representative sampling of the possible variants. However, as the number of modified sites increases, the number of possible variants, and hence the degree of

experimentation required, increases exponentially. Additionally, as plural substitutions are introduced, their interactions with each other and their effects on the structure and function of the protein become progressively less predictable. See Ngo et al. (Computational Complexity, Protein Structure Prediction and the Levinthal Paradox. The Protein Folding Problem and Tertiary Structure Prediction, pp. 433-440 and 492-495; 1994). The artisan would accordingly have no resort save trial-and-error experimentation to determine which of the astronomically large number of possible structural variants had the functional properties of the claimed proteins. Such experimentation would be undue for one skilled in this art. In addition, the specification states that the invention also envisages the possible development of other activators of the EPO receptor, which if developed into EPO analogues can be used in the context of the present invention (page 12, lines 14-30).

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

Claims 21-27 and 30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is reminded of the revision to the Written Description Training Materials, created on March 25, 2008 to supersede and replace the 1999 training materials. For more information, please see www.uspto.gov/web/menu/written.pdf.

The specification fails to provide adequate written description for Gas6 compounds, Gas6 protein analogues, mutants, variants or derivatives thereof or EPO protein analogues, mutants, variants or derivatives thereof. The instant claims are drawn to a genus. According to the specification, the Gas6 compound, Gas6 protein and the EPO protein can encompass one or more amino acid substitutions, deletions, insertions and/or additions made to the protein. The specification and claims do not place any limit on the number of amino acid substitutions, deletions, insertions and/or additions that may be made. Thus, the scope of the claim includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members are permitted. The specification does not describe any members of the claimed genus by complete structure. The specification does not describe the physical or chemical characteristics for substitution variants, deletion variants or insertion variants of Gas6 compound, Gas6 protein or EPO protein. Although the specification states that these types of amino acid changes are routinely made in

the art, the specification and claim do not describe any specific changes to be made. No common structural attributes identify the members of the substitution, deletion and insertion variant genus. Because the disclosure fails to describe the common attributes or characteristics that identify substitution, deletion and insertion variant members of the genus, and because the genus is highly variant, Gas6 compound, Gas6 protein or EPO protein is insufficient to describe the entire genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus, and thus, that the Applicant was not in possession of the claimed genus. The claimed subject matter is not supported by an adequate written description because a representative number of species has not been described.

Claim Objections

Claim 21 is objected to because of the following informalities: The instant claim is not limited to the elected invention. Appropriate correction is required.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Marianne P. Allen/
Primary Examiner, Art Unit 1647

RMD
9/6/08